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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/638,648	08/14/2000	David M. Stern	0575/62097/JPW/JML	9845

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 04/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/638,648	Applicant(s) STERN ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment, filed 2/4/2002, Paper No. 9, has been entered.

Claim 3 has been cancelled; claims 1, 2 and 16 have been amended.

Note that election of the subject to which the method will be administered, a transgenic non-human animal, was made **without** traverse in Paper No. 6. However, after further consideration, the requirement for an election of subject is withdrawn, as such, the Examiner will consider both a transgenic non-human animal and human subject with regard to the claimed invention.

Claims 1, 2 and 4-16 are under current examination.

Any rejection made of record in the prior Office action, mailed 6/20/01, Paper No. 7, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-16 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-16 of copending Application No. 09/992,955. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1, 2 and 4-16 under 35 U.S.C. 112, first paragraph, is maintained because the specification, while being enabling for methods of decreasing cerebral vasoconstriction and ameliorating neurovascular stress in a transgenic mouse which overexpress mutant human amyloid beta precursor protein (APP), bearing the double mutation Lys670Asn and Met 671Leu, (TG APP sw +/- mice) by administration of a soluble receptor for advanced glycation endproduct (sRAGE), the specification does not reasonably provide enablement for methods of decreasing cerebral vasoconstriction, ameliorating neurovascular stress or treatment of amyloid angiopathy in all transgenic non-human animal subjects or human subject by administration of any inhibitor of RAGE. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to a method for decreasing cerebral vasoconstriction in a subject suffering from chronic or acute cerebral amyloid angiopathy which comprises administering to the subject an inhibitor of receptor for advanced glycation endproduct (RAGE) to inhibit transcytosis of amyloid β (Aβ) peptides across the blood-brain barrier in the subject (claim 1). The claimed invention is further directed to a method for ameliorating neurovascular stress in a subject, comprising administering to the subject an inhibitor of RAGE to increase cerebral blood flow (claim 12). The claimed invention is additionally directed to a method of treating amyloid angiopathy in a subject comprising administering to the subject an inhibitor of RAGE to increase cerebral blood flow (claim 16). In particular, the elected inhibitor of RAGE is soluble RAGE (sRAGE).

The specification teaches that administration of an inhibitor of RAGE can be used to treat subjects suffering from chronic or acute cerebral amyloid angiopathy, ameliorate neurovascular stress, or in the treatment of amyloid angiopathy (see p. 7. 1st paragraph, p. 8, paragraphs 1 and 3). The specification specifically teaches the blocking of RAGE in wild-type mice infused with synthetic amyloid-beta (Aβ) peptides by the use of an antibody against RAGE (α-RAGE), and soluble RAGE (sRAGE), which resulted in the suppression of binding and uptake of Aβ in relation to the vessel wall, and inhibited Aβ-induced cellular stress (see Example 1, and

particularly p. 34). The specification teaches that Aβ transport to the brain was significantly inhibited by α–RAGE and abolished by sRAGE and that several other molecular reagents were used to test effects on blood brain barrier (BBB) transport or the binding of Aβ (see p. 32). The specification teaches that transgenic mice that overexpress mutant Aβ precursor protein (APP) (TG APP sw+/- mice) have a significant decrease in basal cerebral blood flow (CBF) values, and that infusion of α-RAGE increased the CBF in these mice. The specification teaches that systemic administration of α-RAGE to these transgenic mice ameliorated cellular stress in the brain (see p. 33, lines 11-29). The specification further teaches that an acute model in mice that had Aβ-induced cellular stress and sustained reductions in CBF was blocked by circulating α-RAGE, and in TG APP sw +/- mice, CBF was reduced by circulating α-RAGE in a dose-dependent fashion (see Example 2).

Although the specification does not explicitly teach the use of sRAGE administration to the TG APP sw +/- mice, Morser *et al.* (WO 97/39121, 23 October 1997) teach that both antibodies to RAGE and soluble RAGE are capable of blocking or inhibiting the interaction between RAGE and its ligands (AGEs) in such diseases as diabetes and Alzheimer's disease (see p. 9, 2nd paragraph and Examples 2 and 4). To this end, one would have a reasonable expectation of success in using sRAGE to increase CBF and ameliorate cellular stress in TG APP sw +/- mice. As such, the claimed invention is enabled for methods for decreasing cerebral vasoconstriction

and ameliorating neurovascular stress in a TG APP sw +/- mouse by the administration of sRAGE as indicated above.

Applicants state that to expedite prosecution of the application, Applicants have amended claim 2 to recite, wherein the subject is a human subject (see p. 10, last paragraph of the Response). Applicants further argue, as the subject is a human subject, this amendment obviated the Examiner's objection regarding the alleged limitations of transgenic technology (see p. 11, 1sst paragraph of the Response). It is noted that Applicants elected a transgenic non-human animal as a species election **without** traverse in Paper No. 6, however, after further consideration, the Examiner withdraws this election requirement, and as such, the claimed invention is examined with regards to both a transgenic non-human animal and a human subject.

Accordingly, the Examiner's prior rejection of claims 1 and 3-16 is maintained, because it is reiterated that the specification fails to teach methods of decreasing cerebral vasoconstriction and amelioration of neurovascular stress in any other transgenic non-human animal other than the exemplified TG APP sw +/- mice. Additionally, the specification fails to provide any relevant teachings or guidance with regard to the production of a transgenic non-human animal as claimed, one of skill would not be able to rely on the state of the transgenic art for an attempt to produce all transgenic animals which over-express mutant human Aβ precursor protein. The Examiner has provided the unpredictable state of the art

for transgenics advanced on pages 5-8 of the prior Office action. Applicants have not provided evidence to overcome the unpredictabilities associated with the art of transgenics, and as such, it would have required undue experimentation for one skilled in the art to predict the results achieved in any host animal comprising and expressing a mutant human amyloid beta precursor protein transgene, the levels of the of the transgene product, the consequences of that produce, and the resulting phenotype.

Applicants traverse the Examiner's comments alleging a lack of guidance or teaching for the treatment of amyloid angiopathy in the present application (see p. 11, 2nd paragraph of the Response). Applicants further state that claim 16 has now been amended to recite a method for treating Alzheimer's disease. Applicants further contend that transgenic mouse models of AD-type pathology support the use of a RAGE inhibitor to decrease cerebral vasoconstriction and ameliorate neurovascular stress in such mice as a therapeutic model for treating AD in a human subject (see p. 12, paragraphs 2-3 of the Response).

Applicants further submit various papers to support that transgenic mice with AD-type pathology may be useful in identifying methods of treatment of AD in a human subject. It is noted that these references, Exhibits B-F, (see pp. 12-16 of the Response) have not been included with Applicants' response, and as such have not been considered. Furthermore, it is noted that Applicants' Supplemental

Information Disclosure Statement, filed 2/21/02, Paper #10, provide the art that was cited by the Examiner in the prior Office action.

However, it is reiterated that the Examiner's comments are not directed to the fact that transgenic mice with AD-type pathology are not useful in the treatment of AD, rather, the Examiner's comments are directed to the claimed embodiment of claim 16 with regard to the decreasing cerebral vasoconstriction in a subject suffering from Alzheimer's disease. The specification has only provided teachings to enable methods of decreasing cerebral vasoconstriction and amelioration of neurovascular stress in transgenic mice which overexpress mutant human amyloid beta precursor protein (APP), bearing the double mutation Lys670Asn and Met 671Leu, (TG APP sw +/- mice) by administration of a soluble receptor for advanced glycation endproduct (sRAGE).

Accordingly, in view of the lack of guidance and direction in the specification for the use of sRAGE to decrease cerebral vasoconstriction or ameliorate neurovascular stress in any other species other than TG APP sw +/- mice, the unpredictable and undeveloped state of the art with respect to transgene behavior in transgenic animal subjects of all species, it would have required undue experimentation for one skilled in the art to carry out the claimed methods, animals and use thereof.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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